Effect of *N*-Bromosuccinimide (NBS) and Other N-Brominating Agents on the Bromination of α,β-Unsaturated Ketones in Methanol

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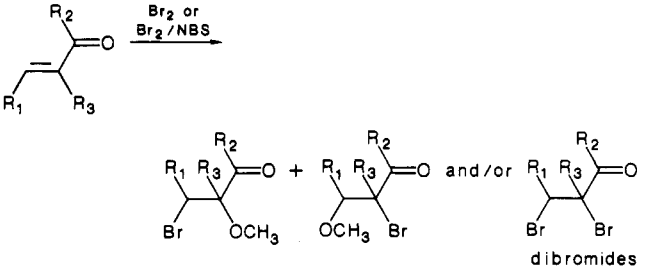
The following α,β-unsaturated ketones were brominated (Br_2) in methanol with and without *N*-bromosuccinimide (NBS): methyl vinyl ketone (**1**), phenyl vinyl ketone (**2**), (*E*)-3-penten-2-one (**3**), methyl isopropenyl ketone (**4**), 2-cyclohexen-1-one (**5**), and 1,4-benzoquinone (**6**). The ratios of Markovnikov:anti-Markovnikov (M:AM) regioisomers were low without NBS and increased when the brominations were conducted in the presence of NBS. The M:AM ratio for **4** remained approximately the same with and without NBS, and **6** gave only dibromide. All of the ketones, except **6**, showed significantly less dibromide with NBS. The rates of bromination of the ketones decreased dramatically with NBS. Selected *N*-bromo amides and **1** gave similar results to those of NBS, showing small variations in the M:AM ratios. The ketones and CH_3OBr/BF_3 gave higher M:AM ratios. The results from bromination of the following esters with and without NBS paralleled the ketones, but with less change in the M:AM ratios: methyl acrylate (**7**), methyl crotonate (**8**), and methyl methacrylate (**9**). Mechanisms of the reactions are discussed. With the ketones, it is suggested that NBS (and the *N*-bromo amides) function by removing acid, thereby causing a change from an acid-catalyzed mechanism to a bromonium ion type mechanism, perhaps involving complexing between the olefin, NBS, and Br_2. The esters probably proceed by the latter mechanism in the presence of NBS.

Many years ago it was observed that, contrary to expectations, the reactions of bromine (Br_2)[1] and chlorine (Cl_2)[2] with certain α,β-unsaturated aldehydes were extremely rapid. Mechanistic explanations for the rapid rates conflicted. Both an acid-catalyzed (enol) mechanism and a carbonyl mechanism were considered.[2] Attack by halogen at the carbon π-bond was probably discounted because of the unexpected fast reactions. About a decade ago, de la Mare tentatively supported the acid-catalyzed mechanism but recommended that more research was needed.[3] Recently de la Mare and co-workers[4] used the acid-catalyzed mechanism to rationalize their data from the bromination of 1,4-benzoquinone in acetic acid. A few years ago we reported on various aspects of the rapid addition of Br_2 to several α,β-unsaturated ketones and speculated on the mechanisms involved.[5]

Recently Whiting and co-workers[6] observed that *N*-bromosuccinimide (NBS) functioned effectively as an acid scavenger in kinetic studies on the bromination of cyclohexene. NBS reacts with hydrogen bromide (HBr) to produce Br_2 and succinimide. It occurred to us that bromination of α,β-unsaturated ketones in methanol in the presence of NBS might proceed quite differently if an acid-catalyzed mechanism was involved. We anticipated that changes might occur in the stereochemistry, regiochemistry and the rates of addition. We have already reported on attempts to use sodium bicarbonate as an acid scavenger in these reactions but because of the low solubility of the base the results were inconclusive.[5]

Results

The reactions and data from the bromination of several α,β-unsaturated ketones in methanol with and without NBS are summarized below and in Table I:



Markovnikov (M) and anti-Markovnikov (AM) methoxy bromides, respectively

These data show that, with the exception of 1,4-benzoquinone (**6**), mixtures of dibromides and methoxy bromides are formed with and without NBS. Bromination in the absence of NBS leads primarily to the anti-Markovnikov (AM)[7] methoxy bromide regioisomer except for ketone **4**. With ketones **1**, **2**, **3**, and **5**, the M/AM ratio increased significantly when the bromination was conducted in the presence of NBS. The presence of NBS resulted in stereospecific addition of Br_2 to ketone **3**. The amounts of dibromide dropped significantly with Br_2/NBS.

In the absence of NBS, the rates of addition were observed qualitatively to be extremely rapid, following a short induction period. Two ketones (**1** and **6**) were examined to determine the effect of NBS on the rate of bromination. Competitive brominations of **1** and the corresponding ester,

(1) Anatakrishnan, S. V.; Ingold, C. K. *J. Chem. Soc.* **1935**, 1396.
(2) White, E. P.; Robertson, P. W. *J. Chem. Soc.* **1939**, 1509.
(3) de la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University Press: London, 1976; p 134.
(4) Atkinson, R. C.; de la Mare, P. B. D.; Larson, D. S. *J. Chem. Soc., Perkins Trans. 2* **1983**, 271.
(5) Heasley, V. L.; Shellhamer, D. F.; Carter, T. L.; Gipe, D. E.; Gipe, R, K.; Green, R. C.; Nordeen, J.; Rempel, T. D.; Spaite, D. W.; Heasley, G. E. *Tetrahedron Lett.* **1981**, *22*, 2467. We no longer believe that a carbonyl mechanism, initiated by attack of halogen on oxygen, is involved in these reactions.
(6) Byrnell, C. J. A.; Coomges, R. G.; Hart, L. S.; Whiting, M. C. *J. Chem. Soc., Perkins Trans. 2* **1983**, 1079. Hart, L. S.; Whiting, M. C. *Ibid.* **1983**, 1087.
(7) The anti Markovnikov regioisomer is defined as having bromine on the α-carbon (adjacent to the carbonyl) and methoxy on the β-carbon; Markovnikov alternates the groups on the α- and β-carbons.

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Table I. Bromination (Br_2) of α,β-Unsaturated Ketones in Methanol with and without NBS

ketones		products (%) methoxybromides M	AM	dibromides	M/AM ratio
methyl vinyl ketone (1):	Br_2	1	14	85	0.07
$R_1 = R_3 = H$, $R_2 = CH_3$	Br_2/NBS	18	76	6	0.23
phenyl vinyl ketone (2):	Br_2	0	16	84	0.00
$R_1 = R_3 = H$, $R_2 = Ph$	Br_2/NBS	28	68	4	0.41
(*E*)-3-penten-2-one (3):	Br_2	1	89[a]	10[b]	0.01
methyl isopropenyl ketone (4):	Br_2/NBS	10[c]	83[c]	7[d]	0.10
methyl isopropenyl ketone (4):	Br_2	6	7	87	0.83
$R_1 = H$, $R_2 = R_3 = CH_3$	Br_2/NBS	49	43	8	1.10
2-cyclohexen-1-one (5):	Br_2	0	100	trace[e]	0.00
R_1 and R_2 are connected as $-(CH_2)_3-$, $R_3 = H$	Br_2/NBS	2	98	trace[e]	0.02
1,4-benzoquinone (6):	Br_2	0	0	100	
R_1 and R_2 are connected as -C(O)CH=CH-, $R_3 = H$	Br_2/NBS	0	0	100	

[a] The methoxy bromide addition was nonstereospecific; diastereomer ratio 81:19. [b] Both dibromide diastereomers were formed: 85:15. [c] The addition was essentially stereospecific; ratio of diastereomers 97:3. [d] The addition was stereospecific. [e] Elimination to give 2-bromo-2-cyclohexen-1-one occurs with and without NBS (%): 27 and 18, respectively. Experiments show that the elimination product is probably derived from the methoxy bromide during the course of the reaction. The dibromide is stable to the reaction conditions.

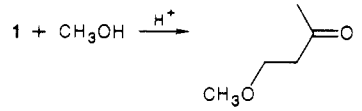
Table II. Regioisomers (%) from 1 with Various Brominating Agents[a]

brominating agent	M	AM
Br_2/NBS	19	81
Br_2/NBA[b]	20	80
Br_2/NDBA[c]	28	72
Br_2/NBMA[d]	24	76
Br_2/2,6-di-*tert*-butylpyridine	14	86
$C_5H_5NHBr_3$[e]	0	100
$Br_2/C_5H_5NHBr_3$	0	100
$C_5H_5NBr_2$[f]	0	100
$Br_2/C_5H_5NBr_2$	17	83

[a] The ratios (%) of MeO, Br:DiBr are as follows: Br_2/NBS, 94:6, Br_2/NBA, 80:20; Br_2/NDBA, 72:28; Br_2/NBMA, 76.24. [b] N^2-Bromoacetamide. [c] *N,N*-Dibromoacetamide. [d] *N*-Bromo-*N*-methylacetamide. [e] Pyridine hydrobromide perbromide. [f] Pyridine dibromide.

methyl acrylate (7), without NBS occurred so rapidly with 1 that no change in the concentration of 7 could be detected. In the presence of NBS, the relative rate of reaction of 1:7 was 2.3 ± 0.2.[8] A semiquantitative study with 6 showed that without NBS the bromination was completed in 15 min and with NBS it was 20% reacted in 1 h.

Acid-catalyzed addition of methanol in the absence of NBS occurred as a side reaction with all of the ketones except 6 to give the β-methoxy ketones. This reaction is outlined below with 1:



No β-methoxy ketones were formed when the brominations were conducted in the presence of NBS, establishing the efficiency of NBS as an acid scavenger.

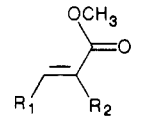
Table II shows the percentages of the methoxy bromide regioisomers of 1 that are formed with the various brominating agents. Dibromides accompanied the methoxy bromides. Br_2/NBS is included for comparison purposes. The data in Table II suggest that the structure of the brominating agent has an affect on the amount of Markovnikov regioisomer. Bromination in the presence of 2,6-di-*tert*-butylpyridine is also reported. 2,6-Di-*tert*-butylpyridine could function as an acid scavenger or form a brominating agent in situ. None of the brominating agents in Table II react with the carbonyl compounds by themselves.[9]

Table III. Bromination of Some α,β-Unsaturated Esters in Methanol

ester		products (%) methoxy bromides (%) M	AM	dibromide	M/AM ratio
7	Br_2	4	21	75	0.19
	Br_2/NBS	16	73	11	0.21
8	Br_2	2	41[a]	57[b]	0.05
	Br_2/NBS	9	85	6	0.11
9	Br_2	12	13	75	0.91
	Br_2/NBS	55	38	7	1.43

[a] Diasteromer ratio 2:98. [b] Diastereomer ratio 3:97.

Data from the bromination in methanol of the following esters, which are structurally analogous to ketones 1, 3, and 4, are shown in Table III: methyl acrylate (7), (*E*)-methyl crotonate (8), and methyl methacrylate (9). The data in



methyl acrylate (**7**): $R_1 = R_2 = H$
methyl crotonate (**8**): $R_1 = CH_3$; $R_2 = H$
methyl methacrylate (**9**): $R_1 = H$; $R_2 = CH_3$

Table III show some increase in the M/AM ratio and a decrease in the amount of dibromides when the brominations are conducted in the presence of NBS. Qualitative observation by GC suggested that the rate of addition to the esters was not affected by NBS.

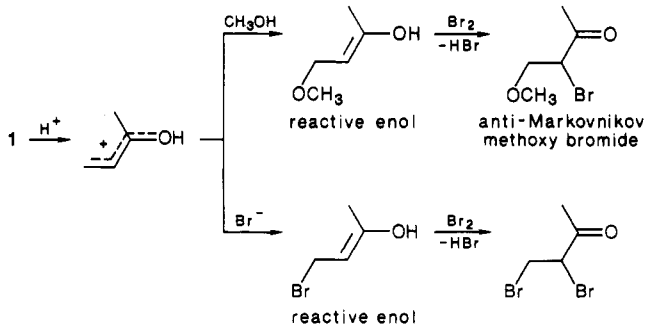
Ketones 1, 2, 3, and 4 were reacted with a solution of HBr and methanol to determine the relative reactivity of bromide ion and CH_3OH toward the conjugate acid of the ketones. Only a trace of β-bromo ketone was formed.

Discussion

In the absence of NBS, we suspect that the bromination occurs by an acid-catalyzed mechanism, as shown below with 1:

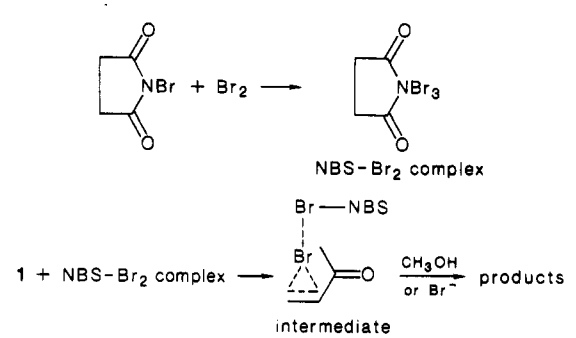
(8) We determined previously[5] that the relative rate of bromination of 1:1-heptene was 4.04.

(9) NBS and the *N*-bromoamides react slightly with the ketones and esters in methanol, probably because of residual Br_2 or acid impurities.



This mechanism is supported by the following data: The rates of bromination of **1** and **6** are greatly reduced in the presence of the acid scavenger NBS;[10] addition to **3** is nonstereospecific; the anti-Markovnikov regioisomer is the major methoxy bromide with all of the ketones except **4**. Apparently with **4**, and to a slight extent with **1** and **3**, there is attack at the carbon π-bond to give the Markovnikov regioisomer. Formation of large amounts of dibromides with **1** and **2** does not appear to correlate with the mechanism, since our data show that the ketones favor attack by methanol rather than bromide ion, which should lead ultimately to methoxy bromide as the major product. We have no explanation for this result.

In the presence of NBS, the close similarity in product ratios between ketones **1**, **3**, and **4** and the analogous esters (**7**, **8**, **9**) suggests that the same mechanism is operative in both cases, probably occurring by attack at the carbon π-bond. This attack may involve formation of a complex between the olefinic bond, NBS (and the *N*-bromo amides), and Br_2 since there are small variations in the ratios of regioisomers with the different brominating agents, as shown in Table II. A possible mechanism is outlined below:



The strongest evidence for complex formation between Br_2 and the brominating agents arises from the fact that pyridine dibromide produces the Markovnikov regioisomer only when the bromination is conducted in the presence of Br_2 (Table II). Stereospecific additions would be anticipated from an intermediate such as the one shown above. Greater Markovnikov addition might result from the fact that the intermediate is less reactive than a bromonion ion or carbocation and attack by methanol at the α-carbon to give the Markovnikov regioisomer is accelerated by the neighboring carbonyl group.[11] In our opinion the results from 2,6-di-*tert*-butylpyridine and Br_2 are best interpreted from the viewpoint that the substituted pyridine and Br_2 react in situ to form a dibromide and then a complex, which brominates like pyridine dibromide/Br_2.[12]

1,4-benzoquinone (**6**) probably fails to give a methoxy bromide adduct, with or without NBS, because methanol is not competitive with bromide ion toward the less reactive intermediate ion. Our data parallel results reported by de la Mare and co-workers[4] which show that bromination of **6** in acetic acid gave only dibromide.

In the absence of NBS, the diBr:MeO,Br ratio decreases in going from ketones **1** and **2** to **3** and **5**. Dubois and Chretien[13] have shown that this ratio is dependent on the extent of carbocation character and decreases with increasing stability of the carbocation. Our data appear to correlate with this principle since ketones **1** and **2** and ketones **3** and **5** should exhibit primary and secondary carbocation character, respectively, in the acid-catalyzed mechanism. A similar, but less pronounced, decrease occurs between esters **7** and **8**. There should be little carbocation character on the α-carbons of **6** because of two carbonyl groups. The diBr:MeO,Br ratio with ketone **4** is similar to **1** and **2**. This is not surprising since little charge should develop on the α-carbon adjacent to the carbonyl group.

Formation of significantly less dibromide in the presence of NBS for ketones **1**, **2**, and **4** probably results from a lower bromide ion concentration since HBr is removed by NBS producing Br_2.

Experimental Section

The α,β-unsaturated ketones were obtained as follows: **1**, **5**, and **6** were purchased from Aldrich Chemical Co. Ketone **3** was obtained from Fairfield Chemical Company. Ketone **4** was purchased from TCI Organic Chemicals. Ketone **2** was prepared from acetophenone and formaldehyde via the Mannich reaction. Its properties were identical with the ketone which we had synthesized previously by oxidation of 1-phenyl-3-propen-1-ol.[5]

The brominating agents and other reagents were obtained as follows: NBS, 2,6-di-*tert*-butylpyridine, and NBA from Aldrich Chemical Company; NDBA[14] from a modification of a literature procedure; $C_5H_5NHBr_3$[15] and $C_5H_5NBr_2$[16] from literature preparations; NBMA was prepared by addition of *N*-methylacetamide to aqueous hypobromous acid, extraction into CH_2Cl_2, drying over $MgSO_4$, and evaporation of the solvent, mp 37 °C. The structure was confirmed by its NMR spectrum and by iodometric titration.

NMR spectra were obtained on a Varian T60A spectrophotometer with $(CH_3)_4Si$ as the reference standard. Mass spectral analyses were obtained at 70 eV on a Hewlett-Pakcard 5790A GC interfaced with an HP5970A mass selective detector. The products were analyzed on a Hewlett-Packard 5790A GC with a 25-m, methyl silicone capillary column. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reaction Conditions. Brominations (3 M Br_2 in CCl_4 or CH_2Cl_2) of the α,β-unsaturated ketones in the absence of NBS were carried out in methanol (0.04 mol fraction) at ice temperatures and to approximately 50% completion. The reaction mixtures were analyzed directly by GC. Alternately, the reaction mixtures were added to water, extracted with CH_2Cl_2, and analyzed. The latter procedure gave lower yields of dibromide. It

(10) Conceivably the Br_2 in solution is complexed with NBS and the reduced rate is due to this factor, not the removal of acid. If this complex is formed, we did not observe it in the UV spectrum.

(11) Lower reactivity of the complex toward methanol would result in greater S_N2 character and, hence, possible acceleration by the neighboring carbonyl group, leading to more Markovnikov regioisomer. Greater acceleration would be anticipated from the ketones than the esters regioisomer. Such acceleration was not observed previously with methyl acrylate (**7**): Heasley, V. L.; Spaite, D. W.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.* **1979**, *44*, 2608.

(12) 2,6-Di-*tert*-butylpyridine and Br_2 appeared to react to give a solid, but decomposition occurred during isolation.

(13) Dubois, J. E.; Chretien, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 3506.

(14) We modified the procedure of S. Wolfe and D. V. C. Awang (*Can. J. Chem.* **1971**, 1398) as follows: NDBA was extracted into CCl_4 from the aqueous reaction mixture and dried. The solvent was removed to leave the crystals.

(15) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*: Wiley: New York, 1967; pp 967–70.

(16) Barili, P. L.; Bellucci, G.; Marioni, F.; Morelli, I.; Scartoni, V. *J. Org. Chem.* **1972**, *37*, 4353.

was established that the dibromides did not react with methanol to give methoxy bromides.

Brominations in the presence of NBS were conducted as follows: to the appropriate mixture of ketone (0.04 mol fraction) and methanol under vigorous stirring was added NBS (or the other brominating agents) at room temperature. The solution was stirred until saturated with a large excess of brominating agent present and then was placed in an ice bath. Sufficient Br_2 was added to react with 25–60% of the α,β-unsaturated ketone.[17] The reactions were allowed to continue until the starting ketone had disappeared as indicated by GC analyses. Similar product ratios were obtained either by direct GC analysis of the reaction mixture or by the following workup procedure: The reaction flask with the excess NBS was attached to a rotary evaporator under vacuum and the solvent and excess Br_2 were removed at room temperature. When the solvent was evaporated, CCl_4 equivalent to the original volume of solvent was added and the excess NBS and succinimide were removed by filtration. Without the presence of excess NBS during the evaporation process, the Markovnikov regioisomers were destroyed or greatly reduced and unidentified byproducts were formed. We assume that NBS prevents the build-up of acid which leads to decomposition.

The ratio of M:AM regioisomers was not affected by the presence of NBS or Br_2. Stability of the Markovnikov methoxy bromide regioisomer from 1 to bromination conditions without NBS was established as follows: 1 was brominated in the presence of NBS to give the Markovnikov regioisomer. This product mixture (M,AM,DiBr) was isolated as described above and mixed with the product mixture from bromination of 1 without NBS. The amount of Markovnikov product did not decrease.

Ketone 1 gave the same ratio of regioisomers at ice and room temperature. The yield of dibromide was lower at room temperature. Ketone 4 was studied only at room temperature. Ketone 2 with NBS was brominated only at room temperature.

Yields (%) of the bromination reactions with and without NBS are, respectively, as follows: 1, 67 and 61; 2, 92 and 93; 3, 92 and 74; 4, 78 and 106. Yields for ketones 5 and 6 were not determined.

Brominations of the esters were conducted in the same manner as the ketones but at room temperature.

Reaction of α,β-Unsaturated Ketones with Methyl Hypobromite, CH_3OBr. The synthesis of CH_3OBr and its reaction with olefins and BF_3 have been described previously.[18] The following percentages of methoxy bromide regioisomers (M and AM) were obtained from the ketones and CH_3OBr/BF_3: 1, 33 and 67; 2, 39 and 61; 3, 28 and 72; 4, 39 and 61; 5, 34 and 64. Ketone 6 and CH_3OBr gave only dibromide and its elimination product. Small amounts of dibromides accompanied the methoxy bromides. Bromo fluorides were also formed. Methyl acrylate (7) and CH_3OBr/BF_3 in CH_2Cl_2 gave the same percentages of regioisomers as 1.

Bromination of Methyl Vinyl Ketone (1). 3-Bromo-4-methoxybutan-2-one. This compound has been described previously.[19]

4-Bromo-3-methoxybutan-2-one. Attempts at isolation of this compound by preparative GC or by distillation led to decomposition. The structure was established by its NMR and the mass spectra and the NMR and mass spectra of its elimination product, 3-methoxy-3-buten-2-one. NMR studies were performed on the product from the reaction of 1 with CH_3OBr since the dibromide was absent in this mixture. The NMR spectrum of the $1/CH_3OBr$ product showed the presence of a second methoxy singlet (3.48 ppm) along with the methoxy singlet (3.35 ppm) of the anti-Markovnikov regioisomer. The percentages of the regioisomers as calculated from the NMR spectrum agreed with the GC data. Mass spectrum of 4-bromo-3-methoxybutan-2-one, m/e (relative intensity): M – CH_3CO (bromine isotopes) 137 (18) and 139 (17), 58 (63), CH_3CO 43 (100). The 137 and 139 fragments were essentially absent in the mass spectrum of the anti-Markovnikov regioisomer. A fragment at m/e 45 (CH_2OCH_3) was major in the anti-Markovnikov regioisomer but absent in the Markovnikov regioisomer. The Markovnikov regioisomer, but not the anti-Markovnikov regioisomer, disappeared upon treatment with triethylamine.

Elimination of the product from $1/CH_3OBr$ with triethylamine in CCl_4 gave a new compound (3-methoxy-3-buten-2-one) whose NMR spectrum showed two methoxy singlets at 3.35 ppm (unreacted anti-Markovnikov regioisomer) and 3.50 ppm and two doublets at 6.26 and 6.78 ppm which indicate vinyl protons. The mass spectrum of this compound confirmed the presence of 3-methoxy-3-buten-2-one, m/e (relative intensity): M 100 (24), M – CH_2O 70 (27), CH_2COCH_3 57 (44), CH_3CO 43 (100).

3,4-Dibromobutan-2-one. This compound has been described previously.[5]

The anti-Markovnikov and Markovnikov regioisomers and the dibromide were separated on the capillary column with the following retention times (min), respectively, by programming from 60 to 120 °C at 5 °C/min: 8.9, 8.4, and 10.4.

Bromination of Phenyl Vinyl Ketone (2). 3-Methoxy-2-bromo-1-phenylpropan-1-one. This compound has been described previously.[19]

3-Bromo-2-methoxy-1-phenylpropan-1-one. All attempts at isolation of this compound and its elimination product, 1-phenyl-2-methoxy-2-propen-1-one, were unsuccessful because of decomposition. The compound and its regioisomer, 2-bromo-3-methoxy-1-phenylpropan-1-one, were separated by capillary GC and mass spectra were obtained. A mass spectrum was also obtained of the elimination product from the compound. An NMR spectrum of the crude reaction mixture, resulting from bromination of 1 (Br_2/NBS) in methanol, showed methoxy singlets at 3.39 and 3.65 ppm in a ratio (%) of 21:79; the methoxy singlet of the anti-Markovnikov regioisomer occurs at 3.39 ppm. The singlet at 3.65 ppm is probably from the compound, based on the correlation of the ratio of peaks with the GC analysis and on a comparison of the chemical shifts of the methoxy protons from 3-bromo-4-methoxybutan-2-one and its regioisomer. The compound disappeared (GC analysis) when treated with triethylamine. Mass spectrum of the compound, m/e (relative intensity): M – C_6H_5CO (bromine isotopes) 137 (3) and 139 (3), C_6H_5CO 105 (100), C_6H_5 77 (56), 58 (66), 51 (24), 50 (9). The fragment at m/e 45 (CH_2OCH_3) was small in the compound and significant in its regioisomer. Mass spectrum of the elimination product (1-phenyl-2-methoxy-2-propen-1-one), m/e (relative intensity): M 162 (14), C_6H_5CO 105 (100), C_6H_5 77 (90), CH_2COCH_3 57 (10).

2,3-Dibromo-1-phenylpropan-1-one. This compound has been described previously.[5]

The anti-Markovnikov and Markovnikov regioisomers and the dibromide were separated on the capillary column with the following retention times (min), respectively, by programming from 150 to 220 °C at 5 °C/min: 9.8, 9.7, and 11.4.

Bromination of (*E*)-3-Penten-2-one (3). 3-Bromo-4-methoxypentan-2-one. This compound has been described previously.[19]

4-Bromo-3-methoxypentan-2-one. This compound was identified by its mass spectrum, m/e (relative intensity): M – CH_3CO (bromine isotopes) 151 (34) and 153 (32), C_4H_8O 72 (89), C_4H_7O 71 (20), C_3H_5O 57 (68), CH_3CO 43 (100). The compound reacted with triethylamine to eliminate HBr.

3,4-Dibromopentan-2-one. This compound has been described previously.[5]

The anti-Markovnikov and Markovnikov regioisomers and the dibromide were separated on the capillary column with the following retention times (min), respectively, by programming from 75 to 100 °C at 25 °C/min: 4.73/4.78 (diastereomers), 4.85 and 5.68/5.70 (diastereomers).

Bromination of Methyl Isopropenyl Ketone (4). 3-Bromo-4-methoxy-3-methylbutan-2-one. This compound was identified by its NMR, IR, and mass spectra and by elemental analysis. NMR: δ 1.90 (s, 3 H), 2.46 (s, 3 H), 3.55 (s, 3 H), 3.62–4.36 (m, 2 H). IR (CCl_4): 1710 (C=O), 2825 (OCH_3) cm^{-1}. Mass spectrum, m/e (relative intensity): C_2HBrO (bromine isotopes) 120 (23) and 122 (23), 75 (40), CH_2OCH_3 45 (41), CH_3CO 43 (100). Anal. Calcd for $C_6H_{11}O_2Br$: C, 36.92; H, 5.64; Br, 41.03. Found: C, 36.80; H, 5.36; Br, 41.10.

(17) Less Br_2 is needed with NBS because as the reaction proceeds HBr (from methoxy bromide formation) is formed which reacts with NBS to produce Br_2. We obtained the same results in the NBS reactions with 1 by adding HBr/CH_3OH (0.1 M) to the reaction mixture.

(18) Heasley, V. L.; Gipe, R. K.; Martin, J. L.; Wiese, H. C.; Oakes, M. L.; Shellhamer, D. F.; Heasley, G. E.; Robinson, B. L. *J. Org. Chem.* **1983**, *48*, 3195.

(19) Heasley, V. L.; Wade, K. E.; Aucoin, T. G.; Gipe, D. E.; Shellhamer, D. F.; Heasley, G. E. *J. Org. Chem.* **1983**, *48*, 1377.

4-Bromo-3-methoxy-3-methylbutan-2-one. This compound was identified by its NMR, IR, and mass spectra and by elemental analysis. NMR: δ 1.40 (s, 3 H), 2.31 (s, 3 H), 3.42 (s, 3 H), 3.50–4.05 (m, 2 H). IR (CCl_4): 1749 (C<<ddbO), 2840 (OCH_3) cm^{-1}. Mass spectrum, *m/e* (relative intensity): M – CH_3CO (bromine isotopes) 151 (63) and 153 (63), 72 (50), 57 (88), 45 (2), 43 (100). Anal. Calcd for $C_6H_{11}O_2Br$: C, 36.92; H, 5.64; Br, 41.02. Found: C, 36.80; H, 5.73; Br, 41.46.

The above regioisomers were isolated from the appropriate bromination mixtures by preparative GC.

3,4-Dibromo-3-methylbutan-2-one. This compound was identified by its NMR and mass spectra and by elemental analysis. NMR: δ 2.07 (s, 3 H), 2.54 (s, 3 H), 3.94 (dd, *J* = 11 Hz, 1 H), 4.34 (dd, *J* = 11 Hz, 1 H). Mass spectrum, *m/e* (relative intensity): M, 246 (1) and 244 (2), M – Br (bromine isotopes) 165 (8) and 163 (8), C_2HBrO (bromine isotopes) 122 (17) and 120 (17), 43 (100), 41 (59), 39 (68). Anal. Calcd for $C_5H_8OBr_2$: C, 24.59; H, 3.28; Br 65.57. Found: C, 24.59; H, 3.37; Br, 65.37.

The anti-Markovnikov and Markovnikov regioisomers and the dibromide were separated on the capillary column with the following retention times (min), respectively, by programming from 75 to 100 °C at 10 °C/min: 5.63, 6.28, and 7.51.

Bromination of 2-Cyclohexen-1-one (5). 2-Bromo-3-methoxycyclohexanone. Attempts to isolate this compound by distillation and preparative GC resulted in decomposition. The structure was established by its mass spectrum, by NMR and IR analyses of a crude reaction mixture, and by the fact that elimination did not occur when treated with triethylamine. The crude product for NMR and IR analyses was isolated from a bromination product (100% completion, no NBS). NBS was added to the reaction product to prevent formation of acid which leads to decomposition during removal of methanol as described earlier. CCl_4 was added to the residue and the NBS was filtered. The NMR and IR spectra were made from this solution. NMR: δ 1.60–3.18 (m, 6 H), 3.40 (s, 3 H), 3.52–4.30 (m, 2 H). IR (CCl_4): 1725 (C=O), 2800 (CH_3O) cm^{-1}. Mass spectrum of the compound, *m/e* (relative intensity): M (bromine isotopes) 206 (0.6) and 208 (0.8), M – Br 127 (100), 95 (18), 85 (33), 83 (24), $C_4H_{10}O$ 74 (82), C_4H_7O 71 (89), 68 (30), 67 (27), 41 (66).

3-Bromo-2-methoxycyclohexanone. This compound was only a trace product in the bromination of **5** in the presence of NBS. It was found in significant quantities (34%) along with its regioisomer in the reaction of **5** with CH_3OBr. GC and GC-MS analyses were performed directly on the reaction mixture because workup resulted in extensive elimination and decomposition. The structure is based entirely on its mass spectrum. The spectrum is similar to that of its regioisomer but with significant changes in intensity. Mass spectrum of the compound, *m/e* (relative intensity): M (bromine isotopes) 206 (3) and 208 (4), M – Br 127 (4), 95 (36), 85 (4), 83 (2), $C_4H_{10}O$ 74 (3), C_4H_7O 71 (48), 68 (18), C_4H_2O 67 (100), 41 (61). We do not feel that the bromomethoxycyclohexanone regioisomers described here represent a mixture of *cis*- and *trans*-4-bromo-3-methoxycyclohexanone stereoisomers since the reaction with CH_3OBr and the other ketones (except **6**) all gave a mixture of regioisomers. We would not anticipate that **5** would react differently.

2,3-Dibromocyclohexanone. This compound was identified by elimination with triethylamine to the known 2-bromo-2-cyclohexen-1-one.[20]

The anti-markovnikov and Markovnikov regioisomers and the dibromide were separated on the capillary column with the following retention times (min), respectively, by programming from 110 to 150 °C at a rate of 5 °C/min: 8.4, 8.1, and 11.2.

Bromination of 1,4-Benzoquinone (6). 2,3-Dibromo-1,4-benzoquinone. This compound has been described previously.[4]

The dibromide gave a retention time of 8.6 min when programmed on the capillary column from 120 to 150 °C at 10 °C/min.

Identification of the β-Methoxy Ketones from Ketones 1, 2, 3, 4, and 5. The β-methoxy ketones were identified as products in the reactions by their mass spectra and in some cases by their NMR spectra. Where NMR spectra were obtained, the compounds were isolated by distillation or preparative GC. In two cases (ketones 1 and 2), the β-methoxy ketones were synthesized unambiguously by adding a drop of H_2SO_4 to the ketones in methanol.

4-Methoxybutan-2-one. This compound was identified by its NMR and mass spectra. NMR: δ 2.12 (s, 3 H), 2.55 (t, 2 H, *J* = 6.0 Hz), 3.28 (s, 3 H), 3.54 (t, 2 H, *J* = 6.0 Hz). Mass spectrum, *m/e* (relative intensity): M 102 (9), M – CH_3 87 (21), 72 (5), 71 (9), M – CH_3OH 70 (8), CH_3OCH_2 45 (71), CH_3CO 43 (100).

3-Methoxy-1-phenylpropan-1-one. This compound was identified by its NMR and mass spectra. NMR: δ 3.09 (t, 2 H, *J* = 6.0 Hz), 3.29 (s, 3 H), 3.73 (t, 2 H, *J* = 6.0 Hz), 7.32–7.58 (m, 3 H), 7.78–8.10 (m, 2 H). Mass spectrum, *m/e* (relative intensity): M 164 (14), M – CH_3OH 132 (15), C_6H_5CO 105 (100), C_6H_5 77 (64), 51 (27), CH_3OCH_2 45 (23).

4-Methoxypentan-2-one. This compound was identified by its NMR and mass spectra. NMR: δ 1.13 (d, 3 H, 6.0 Hz), 2.10 (s, 3 H), 2.30–2.67 (m, 2 H), 3.28 (s, 3 H), 3.42–3.94 (m, 1 H). Mass spectrum, *m/e* (relative intensity): M 116 (0.3), M – 1 115 (0.3), M – CH_3 101 (23), CH_3OCHCH_3 59 (61), CH_3CO 43 (100).

4-Methoxy-3-methylbutan-2-one. This compound was identified by its NMR and mass spectra. NMR: δ 0.61 (d, *J* = 7 Hz, 3 H), 1.94 (s, 3 H), 2.98 (s, 3 H), 2.81–3.21 (m, 3 H). Mass spectrum, *m/e* (relative intensity): M 116 (5), M – CH_3 101 (12), M – CH_3OH 108 (16), 75 (23), $CH_3OCH_2(CH_3)CH$ 73 (4), 69 (19), CH_3OCH_2 45 (80), CH_3CO 43 (100).

3-Methoxycyclohexanone. This compound was identified by its mass spectrum: *m/e* (relative intensity): M 128 (17), M – CH_3OH 96 (51), 71 (100), 58 (97).

Identification of the β-Bromo Ketones from Ketones 1, 2, and 3. The β-bromo ketones were synthesized by adding HBr gas to ketones 1, 2, and 3 in CH_2Cl_2. They were identified by their NMR spectra.

4-Bromobutan-2-one. NMR: δ 2.16 (s, 3 H), 3.04 (t, *J* = 6 Hz, 2 H), 3.53 (t, *J* = 6 Hz, 2 H).

3-Bromo-1-phenylpropan-1-one. NMR: δ 3.12–3.84 (m, 4 H), 6.90–7.56 (m, 3 H), 7.67–8.10 (m, 2 H).

4-Bromopentan-2-one. NMR: δ 1.68 (d, *J* = 7 Hz, 3 H), 2.20 (s, 3 H), 2.81–3.13 (m, 2 H), 4.06–4.73 (m, 1 H).

4-Bromo-3-methylbutan-2-one. NMR: δ 1.28 (d, *J* = 7 Hz, 3 H), 2.31 (s, 3 H), 2.80–3.98 (m, 3 H).

Bromination of Methyl Acrylate (7). Methyl 2-bromo-3-methoxypropanoate,[21] methyl 3-bromo-2-methoxypropanoate,[19] and methyl 2,3-dibromopropanoate[11] have been described previously.

Bromination of (*E*)-Methyl Crotonate (8). *erythro*- and *threo*-methyl 3-methoxy-2-bromobutanoate and *erythro*- and *threo*-methyl 2,3-dibromobutanoate have been described previously.[21] Our NMR data are in general agreement with the reported values.

Bromination of Methyl Methacrylate (9). Methyl 3-Bromo-2-methoxy-2-methacrylate. This compound was identified by its NMR and MS spectra and by elemental analyses (see below). NMR: δ 1.92 (s, 3 H), 3.42 (s, 3 H), 3.95 (s, 3 H). Methylene protons show several peaks (3.55–3.93 ppm) due to conformers which are partially obscured by the other singlets. Mass spectrum, *m/e* (relative intensity): M – CO_2OCH_3 (bromine isotopes) 153 (96) and 151 (100), M – Br 131 (97).

Methyl 2-Bromo-3-methoxy-2-methacrylate. This compound was identified by its NMR and MS spectra and by elemental analysis (see below). NMR: δ 1.98 (s, 3 H), 3.56 (s, 3 H), 3.95 (s, 3 H). Methylene protons show several peaks (3.65–4.20 ppm) due to conformers which are partially obscured by the other singlets. Mass spectrum, *m/e* (relative intensity): M – Br 131 (91), CH_2OCH_3 45 (100). Anal. Calcd for $C_6H_{11}O_3Br$ (mixture of regioisomers): C, 34.29; H, 5.21; Br, 37.91. Found: C, 34.14; H, 5.17; Br, 37.60.

Methyl 2,3-Dibromo-2-methacrylate. This compound was identified by its NMR spectrum and elemental analysis. NMR: δ 2.13 (s, 3 H), 3.86 (d, *J* = 10 Hz, 1 H), 4.02 (s, 3 H), 4.40 (d, *J* = 10 Hz, 1 H). Anal. Calcd for $C_5H_8OBr_2$: C, 24.59; H, 3.28; Br, 65.57. Found: C, 24.59; H, 3.37; Br, 65.37.

Relative Rate Determination. Approximately equimolar amounts of 1 and methyl acrylate in methanol with and without

(20) Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462.

(21) Chartier, H.; Vessiere, R. *Liebigs Ann. Chem.* **1969**, *321*, 313.

NBS were brominated from 10% to 20% completion. The reaction mixture was analyzed by GC for remaining starting material. Relative rates were calculated from the following equation:

$$\frac{k'}{k} = \frac{\log (A_0'/V_0) - \log (A_f'/V_f)}{\log (A_0/V_0) - \log (A_f/V_f)}$$

where A_0' and A_0 represent the original moles of the two compounds, A_f' and A_f represent the final moles of the two compounds, and V_0 and V_f represent the original and final volumes.

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Registry No. 1, 78-94-4; 2, 768-03-6; 3, 3102-33-8; 4, 814-78-8; 5, 930-68-7; 6, 106-51-4; 7, 96-33-3; 8, 623-43-8; 9, 80-62-6; NBA, 79-15-2; NDBA, 598-93-6; NBMA, 51094-87-2; $BrCH_2CH(OCH_3)COCH_3$, 113704-67-9; $CH_3OCH_2CHBrCOCH_3$, 64151-19-5; $BrCH_2CHBrCOCH_3$, 25109-57-3; $BrCH_2CH(OCH_3)COPh$, 113704-68-0; $CH_3OCH_2CHBrCOPh$, 85083-55-2; $BrCH_2CHBrCOPh$, 51011-65-5; (R*,R*)-$CH_3CHBrCH(OCH_3)COCH_3$, 113725-87-4; (R*,S*)-$CH_3CHBrCH(OCH_3)COCH_3$, 113704-78-2; (R*,R*)-$CH_3CH(OCH_3)CHBrCOCH_3$, 85083-56-3; (R*,S*)-$CH_3CH(OCH_3)CHBrCOCH_3$, 85083-57-4; (R*,R*)-$CH_3CHBrCHBrCOCH_3$, 113704-69-1; (R*,S*)-$CH_3CHBrCHBrCOCH_3$, 113704-79-3; $BrCH_2C(OCH_3)(CH_3)COCH_3$, 113704-70-4; $CH_3OCH_2CBr(CH_3)COCH_3$, 113704-71-5; $BrCH_2CBr(CH_3)COCH_3$, 85526-21-2; CH_3OBr, 28078-73-1; $C_5H_5NHBr_3$, 39416-48-3; $C_5H_5NBr_2$, 6081-86-3; $BrCH_2CH(OCH_3)COOCH_3$, 60456-17-9; $CH_3OCH_2CHBrCOOCH_3$, 27704-96-7; $BrCH_2CHBrCOOCH_3$, 1729-67-5; $CH_3CHBrCH(OCH_3)COOCH_3$, 113704-75-9; (R*,R*)-$CH_3CH(OCH_3)CHBrCOOCH_3$, 26839-92-9; (R*,S*)-$CH_3CH(OCH_3)CHBrCOOCH_3$, 29247-01-6; (R*,R*)-$CH_3CHBrCHBrCOOCH_3$, 26708-42-9; (R*,S*)-$CH_3CHBrCHBrCOOCH_3$, 22426-04-6; $BrCH_2C(OCH_3)CH_3COOCH_3$, 82270-54-0; $CH_3OCH_2CBr(CH_3)COOCH_3$, 113704-76-0; $BrCH_2CBr(CH_3)COOCH_3$, 3673-79-8; $CH_2{=}C(OCH_3)COCH_3$, 51933-10-9; $CH_2{=}C(OCH_3)COPh$, 54123-71-6; $CH_3O(CH_2)_2COCH_3$, 6975-85-5; $CH_3O(CH_2)_2COPh$, 55563-72-9; $CH_3CH(OCH_3)CH_2COCH_3$, 13122-52-6; $CH_3OCH_2CH(CH_3)COCH_3$, 14539-67-4; $Br(CH_2)_2COCH_3$, 28509-46-8; $Br(CH_2)_2COPh$, 29636-75-7; $CH_3CHBrCH_2COCH_3$, 113704-77-1; $BrCH_2CH(CH_3)COCH_3$, 109539-55-1; 3-bromo-2-methoxycyclohexanone, 113704-72-6; 2-bromo-3-methoxycyclohexanone, 113704-73-7; 2-bromo-2-cyclohexen-7-one, 50870-61-6; 2,3-dibromo-1,4-benzoquinone, 25705-58-2; 2,6-di-*tert*-butylpyridine dibromide, 113704-74-8; 3-methoxycyclohexanone, 17429-00-4.

Transfer of the Diethoxyphosphoryl Group [$(EtO)_2PO$] between Imidazole and Aryloxy Anion Nucleophiles

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Rate constants have been measured for reaction of imidazole with aryl diethyl phosphate (k_1) and of aryloxy

anions with *N*-(diethoxyphosphoryl)imidazolium ion (k_{-1}) in aqueous solution at 25 °C; they obey the following linear Brønsted equations: $\log k_1 = -1.02pK_{ArOH} + 1.83$ ($n = 6$, $r = 0.989$); $\log k_{-1} = 0.85pK_{ArOH} - 0.48$ ($n = 10$, $r = 0.957$). The value of β_{eq} (1.87) obtained from β_{lg} and β_{nuc} supports a previously determined value (1.83) for the transfer of the neutral phosphoryl group [$(HO)_2PO$] from phenolate ion nucleophiles. The pK_a of (diethoxyphosphoryl)imidazolium ion is 6.04. The equilibrium constant for reaction of 4-nitrophenyl diethyl phosphate with imidazole is 5.9×10^{-6}; in the case of the aryl ester from phenol with $pK_{ArOH} = 4.34$ the equilibrium constant is calculated to be unity. The Brønsted β_{eq} data are used to calibrate effective charges derived from previously measured β_{lg} values for attack of nucleophiles at phosphorus bearing phenolate ion leaving groups.

Polar substituent effects on reaction rates and equilibria remain one of the most useful tools for investigating charge changes in organic reactions.[1] The effects, when compared with those for a standard equilibrium involving an ionization, give rise to the quantity defined as the effective charge change[1,2] from reactant to transition or product states. Effective charge values have little significance when considered alone;[1] in order to apply effective charge changes to investigate the extent of bond fission in a transition state, it is necessary to calibrate them with the change in charge on the atom in question when the reaction is completed. The polar substituent effect on such a calibration equilibrium compared with that of the standard ionization equilibrium is often quantified as a β_{eq} parameter (provided the reaction is amenable to the Brønsted approach).[1]

The value of β_{eq} has been determined by a number of different methods for carbonyl group (RCO) transfer between various types of nucleophile, and such values are relatively well understood. β_{eq} values for transfer of the phosphoryl group (PO_3^{2-}) between substituted pyridines have been determined by two independent groups[3,4] and these values are in agreement, but there is only one value of β_{eq} for transfer between oxyanions that has been estimated by a bonafide method.[5] Values of β_{eq} for transfer of phosphoryl groups between nucleophiles are very important in studies of bonding and charge in phosphorylation reactions in solution especially as there are now many values of β_{nuc} and β_{lg} in the literature that are available

(1) (a) Williams, A. *Acc. Chem. Res.* **1984**, *17*, 425. (b) Thea, S.; Williams, A. *Chem. Soc. Rev.* **1986**, *15*, 125.
(2) Jencks, W. P. *Cold Spring Harbor Symp. Quant. Biol.* **1971**, *36*, 1.
(3) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597.
(4) Bourne, N.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 7591.
(5) Bourne, N.; Williams, A. *J. Org. Chem.* **1984**, *49*, 1200.

0022-3263/88/1953-2204$01.50/0